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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,022	09/17/2003	Dennis M. Klinman	4239-66899	7954

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EXAMINER	
HORNING, MICHELLE S	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
10/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,022	KLINMAN ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/17/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6,8-22 and 25-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8-22 and 25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to communication filed 7/17/2009. The status of the claims is as follows: claims 1, 2, 4-6, 8-22 and 25-34 are pending and **all** claims are under current examination. The elected species is SEQ ID NO: 1 (in which SEQ ID NO: 177 is encompassed); see arguments filed 12/12/2006.

Any objection or rejection not reiterated herein has been withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/17/2009 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 depends from claim 1 and is drawn to a K oligonucleotide. However, claim 1 is drawn to a D oligonucleotide. Appropriate correction is required.

Specification

The use of the trademarks, including CRIXIVAN and VIRACEPT, has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Note that stated trademarks above are merely examples and all trademarks should be capitalized throughout the specification.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151-IDS), Lu et al. (*Vaccine*, 1997) and Cho et al. (*Nature Biotechnology*, 2000).

Klinman teaches a method of increasing an immune response in a subject using an immunostimulatory D oligonucleotide wherein the sequence is represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3' (see Abstract, col.2, col. 3, lines 5+ and col. 12; see instant claim 1, *in part*). The authors disclose SEQ ID NO: 1 which meets the structural limitations of both SEQ ID NO: 1 and SEQ ID NO: 177 of the instant application (see instant claims 8, 21, 26, 27and 31). One embodiment teaches Pu1 Py2 CpG Pu3 Py4 as having all phosphodiester bases (col. 13, lines 30+; instant claims 9 and 10). The authors also describe using a chimera of phosphodiester and phosphothioate bases in X1X2X3 and X4X5X6 (see col. 13, lines 31+; instant claims 11-13). Klinman teaches X1 X2 X3 Pu1 Py2 and Pu3 Py4 X4 X5 X6 are self-complementary in an embodiment (col. 14, lines 1-2; instant claim 14). K oligonucleotides are described in col. 12 comprising the formula found in the instant claim 22.

While Klinman teaches the structure of the immunostimulatory sequence as claimed, Klinman does not teach a method of increasing an immune response to an *opportunistic infection in an immunocompromised subject* having *SIV or AIDS* wherein the *secondary infection is a viral infection*.

Lu et al. describes opportunistic infections in SIV-infected Macaques (see abstract). The author states that "Opportunistic infections are frequently found in AIDS patients and SIV challenged macaques" (see p. 921, col. 2). Table 1 provides a summary of opportunistic infections in macaques, including pneumonia, a viral infection (see instant claim 15).

Cho et al. describes the use of immunostimulatory DNA sequences containing unmethylated CpG motifs for stimulating host defense in subjects with chronic immunosuppression and AIDS (see abstract). Cho et al. provide that immunostimulatory DNA sequence-based vaccines have a clinical application in AIDS and other immunodeficiencies and these vaccines may provide protection against opportunistic infection (see p. 513, col. 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the CpG-containing sequences described by Klinman in a method for treating selected immunocompromised subjects with opportunistic infections and assessing the resulting responses. One of ordinary skill in the art at the time the invention was made would have been motivated to use a known immunostimulatory CpG sequence (as taught by Klinman) for the advantage of stimulating host defense in AIDS, SIV and chronic immunosuppression (see Cho and Lu). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary skill in the art. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 5 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151), Lu et al. (*Vaccine*, 1997) and Cho et al. (*Nature Biotechnology*, 2000) as applied to claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31

above, and further in view of US Patent No. 6326007 (Yilma) and Bielorai et al. (*Bone Marrow Transplantation*, 2000) and

The combination of Klinman, Lu and Cho teach a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising administering immunostimulatory oligonucleotides, including a sequence represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3'.

The combination of Klinman, Lu and Cho does not teach a subject that is immunocompromised as a result of HIV-2 or chronic granulomatous disease.

Yilma describes HIV-2 as being associated with both immunodeficiency and opportunistic infections (see col. 1, lines 53+).

Bielorai et al. describes chronic granulomatous disease as a primary immunodeficiency disorder characterized by susceptibility to bacterial and fungal infections or opportunistic infections (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase an immune response in an immunocompromised subject (as taught by the combination of Klinman, Lu and Cho) having either HIV-2 or granulomatous disease using known CpG-containing sequences. One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the advantage of enhancing host survival in immunosuppressed subjects to provide protection against opportunistic infections (see Cho). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success

given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary skill in the art. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 4, 16, 25, 28, 29 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151), Lu et al. (*Vaccine*, 1997) and Cho et al. (*Nature Biotechnology*, 2000) as applied to claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31 above, and further in view of Raz (US Patent No. 6552006), Hamour et al. (J. Infect., 1998 ABSTRACT ONLY) and Glaser et al. (Clin. Infect. Dis., 1994 ABSTRACT ONLY).

The combination of Klinman, Lu and Cho teach a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising administering immunostimulatory oligonucleotides, including a sequence represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3'.

The combination of Klinman, Lu and Cho does not teach treating secondary infections, specifically *Leishmania* and *Listera*, or HIV-1 infection.

Raz teaches immunomodulatory nucleic acids comprising CpG motifs enhance host survival against *Listeria* and *Leishmania* (col. 3, lines 34+; instant claims 16 and 28).

Hamour et al. discloses that *Leishmania* is a well recognized opportunistic infection in patients with the HIV-1 (see abstract).

Glaser et al. is cited to demonstrate that *Listeria* is a known opportunistic infection among HIV-infected subjects (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase an immune response in an immunocompromised subject (as taught by the combination of Klinman, Lu and Cho) to either *Listeria* or *Leishmania* using known CpG-containing sequences. One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the advantage of enhancing host survival against known opportunistic infections *Listeria* and *Leishmania* (see Raz). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary skill in the art. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 17, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151), Lu et al. (*Vaccine*, 1997) and Cho et al. (*Nature Biotechnology*, 2000) as applied to claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31 above, and further in view of Davis et al. (*Vaccine*, 2000) and Chung et al (*Antivir. Chem Chemother.*, 2001 ABSTRACT ONLY).

The combination of Klinman, Lu and Cho teach a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising administering immunostimulatory oligonucleotides, including a sequence represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3'.

The combination of Klinman, Lu and Cho does not teach treating hepatitis B as the secondary infection in an immunocompromised subject.

Davis et al. evaluated the immune response following CpG ODN administration and determined that CpG ODN greatly increased the titers of antibody against HBsAg in blood (see abstract, p. 1921, col. 2). Note that this meets the limitations of evaluating the immune response to hepatitis B antigen comprising determining the amount of antibodies to hepatitis B in the subject's serum (instant claims 33-34).

Chung et al. is cited to show that HBV infection is an HIV-associated opportunistic infection (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase an immune response in an immunocompromised subject (as taught by the combination of Klinman, Lu and Cho) to HBV using known CpG-containing sequences. One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the advantage of stimulating host defense in immunocompromised subjects against known opportunistic infections including HBV. Further, the prior art teaches that CpG administration successfully increases antibody titers against HBsAg (see Davis et al.). One of ordinary skill in the

art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary skill in the art. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 4 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151), Lu et al. (*Vaccine*, 1997) and Cho et al. (*Nature Biotechnology*, 2000) as applied to claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31 above, and further in view of Hamour et al. (J. Infect., 1998 ABSTRACT ONLY) and Fraternale et al. (*JAIDS*, 2000).

The combination of Klinman, Lu and Cho teach a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising administering immunostimulatory oligonucleotides, including a sequence represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3'.

The combination of Klinman, Lu and Cho does not teach a method of further administering HAART or AZT to subjects with HIV-1.

Hamour et al. discloses that *Leishmania* is a well recognized opportunistic infection in patients with the HIV-1 (see abstract).

Fraternale et al. describes antiretroviral therapies in HIV-1 patients, including HAART and AZT (see abstract and whole document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase an immune response in an immunocompromised subject (as taught by the combination of Klinman, Lu and Cho) having an HIV-1 infection using known CpG-containing sequences and known antiretroviral drugs, including HAART and AZT. One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the advantage of stimulating host defense in immunocompromised subjects against opportunistic infections and for the treatment of HIV-1 infection itself. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary skill in the art. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Declaration

The declaration under 37 CFR 1.132 filed 7/17/2009 is sufficient to overcome the rejection of claims 1,2,4-6,9-22 and 25-34 based upon the Klinman (US Patent No. 6977245) as a primary reference and all rejections previously cited relying on Klinman (US Patent No. 6977245) as the primary reference.

However, new grounds of rejection as set forth above have been made relying on WO/0061151 (which is a WO equivalent to Klinman US Patent No. 6977245), which has

a publication date of Oct. 19, 2000, and therefore qualifies as prior art under 35 USC 102(b). Thus, the WO/0061151 cannot be properly obviated via a declaration of conception to overcome a prior art date based on 35 USC 102(e) asserting that the current inventors were the sole inventors of the claimed subject matter since it qualifies as prior art under 35 USC 102(b) having a publication date more than one year prior to the earliest US priority of the instant application. Note, the earliest US priority granted for the instant application is 9/18/2002 and the cited WO/0061151 was published on 10/19/2000.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EMILY M LE/
Primary Examiner, Art Unit 1648

/M. H./
Examiner, Art Unit 1648